ALTERATION OF HUMAN CONSCIOUSNESS BY NITROUS OXIDE AS ASSESSED BY ELECTROENCEPHALOGRAPHY AND PSYCHOLOGICAL TESTS

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THE nature of consciousness has been debated from early times, but more recently research has been concentrated on two major approaches to this ancient problem. The psychologist, attempting to introduce measurement, has sought to break down the concept of consciousness into facets that can be quantitated by psychologic tests. This method has been used by Simon and Emmons,[1] who noted "that two measures that are believed to be highly correlated with the degree of consciousness in normal and motivated individuals are (1) the ability to recognize and report the occurrence of particular stimuli to which they have been instructed to attend, and (2) the ability to remember and later to recall these stimuli."

On the other hand, the neurophysiologist has sought some kind of physical change in the nervous system that might correlate with alteration in consciousness. An important advance in this direction was made by Berger,[2] who showed that electrical activity of the brain as measured by electroencephalography changes specifically and characteristically with alterations of consciousness such as sleep and anesthesia. A further encouragement for neurophysiologic investigation has been the work of Magoun,[3] who has demonstrated that regulatory systems in the brain stem influence both conscious behavior and EEG impulses.

Simon and Emmons[1] have utilized these two avenues of study in their investigation of phases of sleep and the EEG. It was anticipated that studies correlating levels of consciousness with the EEG when the latter was altered by drug action might provide further clues to the mind-brain relationships and the validity of EEG measures of this complex function. Nitrous oxide was chosen for this purpose, because it provides a relatively safe, pleasant, controllable, and rapid means of changing the level of consciousness in volunteer subjects. Reports of investigations with this agent range from the original description by Sir Humphrey Davy[4] to recent accounts of careful work by Steinberg and co-workers[5-7] which includes tests of cognition, anxiety, time perception, and behavior. The effect of nitrous oxide on the EEG has been studied by Beecher and McDonough[8] and by Courtin and associates.[9] However, these studies were made at anesthetic levels and are not immediately relevant to the present investigation. Furthermore, no detailed quantitation of EEG findings was made.

The presently reported investigation, therefore, was an attempt to accomplish a detailed quantitation of psychologic and electroencephalographic changes related to nitrous oxide and a careful evaluation of possible correlations of data obtained by these two kinds of study.

METHODS AND RESOURCES

Eighteen volunteer subjects participated in the study. Every subject underwent a sequence of tests while breathing compressed air and a comparable sequence while breathing a mixture containing 30 per cent nitrous oxide and 70 per cent oxygen. On each occasion the subject was permitted 10 minutes for adapting to the unknown gas; then the first group of psychologic tests were administered, and after this an EEG was recorded. The mask was removed and the subject recorded his introspective report of his reactions during the experiment. Testing of delayed recall and recognition completed the data.

Subjects. A group of 18 adults—10 men and eight women—volunteered to participate in the study. Their ages ranged from 18 to 50 years, averaging 30.5 years. Seven of the

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men were physicians, two were highly trained psychologists, and one was a nurse anesthetist. Two of the women were graduate psychologists and six were EEG technicians. All were capable, productive people; and average or more than average intelligence was assumed for them.

The cooperation of the subjects was obtained by invitation to "assist in the study of the effects of light concentrations of nitrous oxide." Obviously certain drug effects would be anticipated by this sophisticated group, but no comment of the subjects regarding use of compressed air or effects of nitrous oxide was discussed by the investigators until the collection of data was completed.

All subjects accepted for this experiment had an alpha rhythm at least moderately well-developed in their resting EEG record.

Materials. GAS: The 30 per cent concentration of nitrous oxide was utilized because frequent nausea and occasional vomiting were encountered with higher concentrations.

Special mixtures of nitrous oxide with oxygen were prepared and were administered through the A.F. 14 face mask. The percentage composition of the mixtures was checked by means of a Beckman oxygen meter and found accurate within 1 per cent. The gas cylinders were meticulously disguised and the gases were scented with peppermint oil.

TESTS OF VERBAL AND VISUAL RETENTION: The retention tests were of three types. The first utilized a meaningful short story taken from the Wechsler Memory Scale, Forms I and II.[10] Each selected story consisted of 22 to 23 items. After having heard the story, the subject was asked to repeat it; and the record of his recall was checked for those items. Also, for every story a multiple-choice test of 22 to 23 questions was prepared, each containing the key word chosen from one item and four words not from the story. The subject was instructed to omit the answer if he had no recognition of the correct word.

The second type of test material consisted of five design pairs drawn on five separate cards and two recognition strips, as constructed and utilized as in the Hunt Minnesota Test for Organic Brain Damage.[11] Two comparable sets of five design pairs were made, and the two sets were interchanged regularly on different test days to assess their comparative testing value.

The third test consisted of six nonsense syllables of low associational value from standardized tests prepared by Melton and Malmo.[12]

INTROSPECTIVE RECORDS: At the end of each testing session, the subject was asked to retire to a private room and complete an introspection sheet bearing this heading:

> Please report as completely as possible your experiences while breathing the gas. Particularly note the following: (1) Physical sensations or changes. If any were noted, grade them minimal, mild, moderate, severe. (2) Your feelings about your test performance. (3) Any mental or emotional changes, including mood, thought processes, fantasies, etc. (4) Any further subjective experiences. (5) Your reaction to the experiment.

EQUIPMENT UTILIZED IN EEG STUDY: An eight-channel Grass EEG inkwriting oscillograph (Type C, time constant 0.18 second) was utilized in conjunction with an Ediswan Walter automatic frequency analyzer in these studies. Two telegraph keys, one being operated by the experimenter and a second by the subject to respond to the sound from the experimenter's relay, were used for arousal stimulus. Both stimulus and response were recorded by inkwriters on the EEG record. Experience showed that this device was necessary because without it the quietness and the recumbent position used during the EEG recordings induced patterns of drowsiness, which had marked effects on the EEG.

Procedure. The actual tests began 10 minutes after the subject started breathing the gas. Orientation as to time, place, and person was checked, and for simple tests of mental control the subject was asked to count from one to 53 by fours and to repeat the alphabet as rapidly as possible.

Then the short story was read to the subject, and his immediate retelling of it was recorded verbatim.

Next, after careful instruction as to the method of the design test, he was shown the five design pairs at the rate of one pair every 3 seconds. Then the cards were shuffled and the stimulus member of the design pair was presented with repeat instructions to select its mate from the two recognition strips. Five seconds were allowed for the selection. The number of trials necessary to learn the five design pairs and the number of errors per trial were recorded, the series being repeated until the subject completed it twice successively without error, or had tried 15 times.

After that, the subject was given fresh instruction on the technique of serial-anticipation learning utilized in the nonsense-syllable tests. (Each subject had had three practice trials on comparable tests prior to the test day.) He was instructed to learn the syllables in order, so that he could recite them twice without errors. The cards bearing individual syllables were presented at the rate of one every 3 seconds. On the second run each syllable served as a stimulus for anticipation of its successor. The subject was instructed to spell the syllable out during memorization as suggested by Luh.[13] Again the numbers of trials and of errors per trial were recorded.

If the criterion of success was not met in 15 trials, the attempt to learn the designs or syllables was discontinued. (Preliminary studies had revealed that many subjects achieved success after 10 to 12 trials, but beyond 15 trials motivation became so impaired that further testing was of limited value.) Those subjects who failed to learn the design series or the syllable series in 15 trials were given a score of 15 on the trial data. In data used to evaluate the total errors per subject in each specified test (table 1), their errors were recorded as the total number of errors in the 15 trials.

When these tests were completed, the subject was asked to recline on a bed and instructed to remain awake but relaxed while an EEG was made. Since 20-minute EEG runs were recorded, it was necessary to use the telegraph-keys mentioned above to arouse the subject. Through the recording period, the experimenter tapped out a simple but varying signal, and the subject was required to reproduce the signal with his key.

Preliminary trial had suggested that the observed EEG effects due to nitrous oxide were particularly prominent in the frontal and occipital leads. The five pairs of electrodes were spaced evenly along two parallel lines running 1½ inches right and left of the midline from inion to glabella. The epoch averager on the Walter automatic analyzer was set to integrate over a 30-second interval in this study. Longer intervals proved unsatisfactory because they limited unduly the selection of recording to exclude those parts in which slow waves due to eye blink had intruded.

In most instances, the face mask was removed shortly before the end of the EEG recording.

Writing of the introspective report followed.

Then—about 20 minutes after removal of the mask and about 45 minutes after the story had been heard—the subject was asked again to repeat the story (for a second recording) and was given the multiple-choice questions as tests of delayed recall and recognition.

In preparation for statistical study, as nearly as possible 10 consecutive minutes of analyzed record were counted. The 24 component frequencies ranging from 1.5 to 30 cycles per second (cps) were divided into five bands. The delta band included the frequencies from 1.5 to 3.5 cps, theta those from 4 to 7, alpha from 8 to 13, intermediate fast from 14 to 18, and beta from 20 to 30.

The activity during each minute in each of the five bands was tabulated. Thus it was possible to compare the total activity and average per minute in the control record with the total activity and average per minute in the gas record for each component band.

The records were read also by one of the authors (R.G.B.) and his visual analyses were tabulated.

Results

Psychologic Tests. All 18 subjects completed the compressed air and nitrous oxide studies. The initial analysis of the data included the calculation of means, standard deviations, and t's from the group records on each of the three mental tests given during breathing of air and of 30 per cent nitrous

TABLE 1

DATA FROM TESTING BY STORIES, DESIGNS, AND NONSENSE SYLLABLES WITH AIR AND WITH 30 PER CENT NITROUS OXIDE

Subject and Sex	Story, Immed. Recall	Designs		Syllables		
		Trials	Errors	Trials	Errors	
1. M	16/23	5	10	4	8	Air
	4/22	14	21	5	18	Gas
2. M	17/23	3	4	5	12	Air
	8/22	13	21	15	51	Gas
3. M	20/23	1	0	4	6	Air
	14/22	15	48	13	36	Gas
4. M	13/23	3	3	2	4	Air
	8/22	5	8	5	15	Gas
5. F	12/23	2	1	5	9	Air
	7/22	7	14	9	22	Gas
6. F	15/23	4	4	4	12	Air
	5/22	6	14	12	31	Gas
7. F	12/23	2	1	5	9	Air
	4/22	9	19	7	19	Gas
8. F	8/23	3	2	2	2	Air
	6/22	10	19	8	16	Gas
9. M	14/23	1	0	5	11	Air
	9/22	10	10	12	22	Gas
10. M	12/23	5	8	11	25	Air
	10/22	15	53	15	62	Gas
11. M	14/23	2	1	4	9	Air
	7/22	5	9	13	31	Gas
12. M	12/23	4	4	5	8	Air
	11/22	14	24	15	54	Gas
13. F	14/23	1	0	6	12	Air
	8/22	6	9	13	41	Gas
14. M	20/23	6	7	8	24	Air
	5/22	3	3	16	48	Gas
15. F	13/23	7	17	6	19	Air
	9/22	10	22	9	24	Gas
16. F	13/23	2	2	7	12	Air
	4/22	8	16	None	None	Gas
17. M	12/23	7	17	7	21	Air
	5/22	15	45	15	62	Gas
18. F	19/23	3	5	5	12	Air
	8/22	3	4	5	12	Gas

TABLE 2

PERFORMANCES ON COMPARABLE MENTAL TESTS IN TWO SERIES OF SUBJECTS UNDER DIFFERENT EXPERIMENTAL CONDITIONS

Conditions	Measures	Stories*	Designs†	Syllables†
Presently Reported Series				
Air	Mean (S.D.)	14.2 (3.2)	3.4 (1.3)	5.2 (2.1)
30% N_2O	Mean (S.D.)	7.7 (2.7)	9.3 (4.2)	11.8 (6.6)
	t34	4.6	5.4	5.5‡
	p	.001	.001	.001
Series of Parkhouse and Associates[14]				
Air	Mean	11.9	3.3	4.7
30% N_2O	Mean	7.4	6.7	9.7
	t44	6.9	3.6	5.5

* Test of immediate recall of 23-item meaningful stories.
† Number of trials required to achieve two perfect series of matching (designs) or recitations (of syllables). Subjects failing to achieve the standard in 15 trials were given 15 arbitrarily as their final score.
‡ t32.

oxide. The subjects who failed to meet the designated criterion of success with design pairs and nonsense syllables (two consecutive perfect recitations of the test material) were included in these calculations, their scores being defined arbitrarily as 15. The basic data from the psychologic tests are presented in table 1. The results of this analysis, which appear (along with some material from another study) in table 2, demonstrate the marked impairment in mental performance during breathing of nitrous oxide.

The degree to which breathing nitrous oxide changed performance from the standard established during breathing air, and the wide distribution of impairment from minimal to serious among the subjects when breathing nitrous oxide, are shown in figure 1. It is noteworthy that three to five subjects suffered such impairment that they continued to make errors through 15 trials of the simple tests. The impairment was accentuated when the subject lay supine with eyes closed. Under these conditions nearly all subjects commented that the effect of the gas seemed "much stronger" in that they tended to become very sleepy unless continuously stimulated, and many felt dissociated from their immediate environment.

Comparison of each subject's immediate recall of meaningful stories while breathing nitrous oxide and while breathing air showed no significant correlation between the performances under the two circumstances (fig.

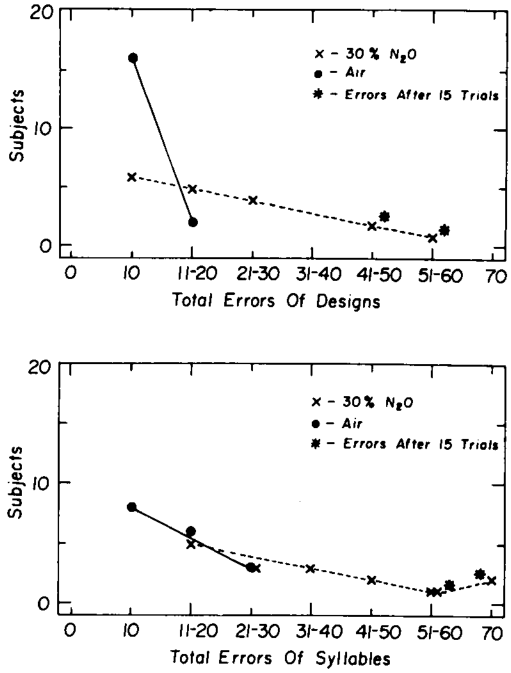

FIG. 1. Numbers of subjects scoring at the various levels on selected mental tests with breathing of air and of 30 per cent nitrous oxide.

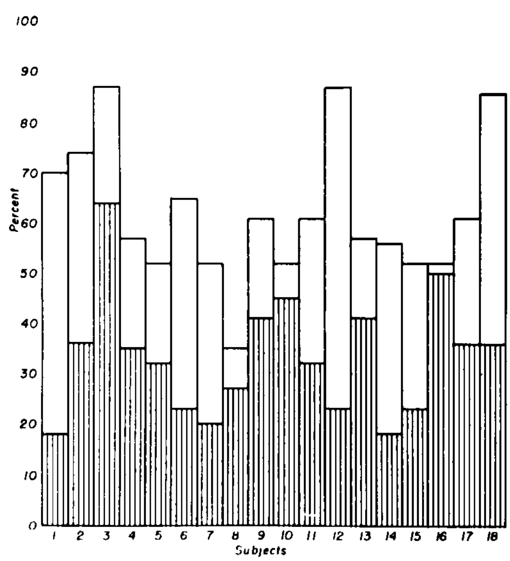

FIG. 2. Percentage immediate recall of story with breathing of air (total bar) and of 30 per cent nitrous oxide (lined bar).

2). Spearman's[15] rank difference correlation factor was 0.15 (no correlation) when immediate recall on the test with gas was ranked against immediate recall on the test with air.

Possible amnesic effects associated with breathing of nitrous oxide were evaluated by the retesting on the meaningful story 30 minutes after administration of the gas was discontinued. Verbal recall was recorded verbatim, and recognition was evaluated by testing with the 23 multiple-choice items.

Scores from the immediate and delayed testing of recognition associated with breathing of air and of gas were compared (fig. 3). Analysis of the data from the meaningful-story testing with 30 per cent nitrous oxide revealed two general effects. First, registration of the stimulus (story) was significantly impaired. Both the immediate recall and the delayed recall and recognition of the story were significantly decreased by administration of the gas. Second, figure 3 shows that the slope of the line on the recall tests with nitrous oxide is steeper than the forgetting rate represented by the slope for the comparable control tests.

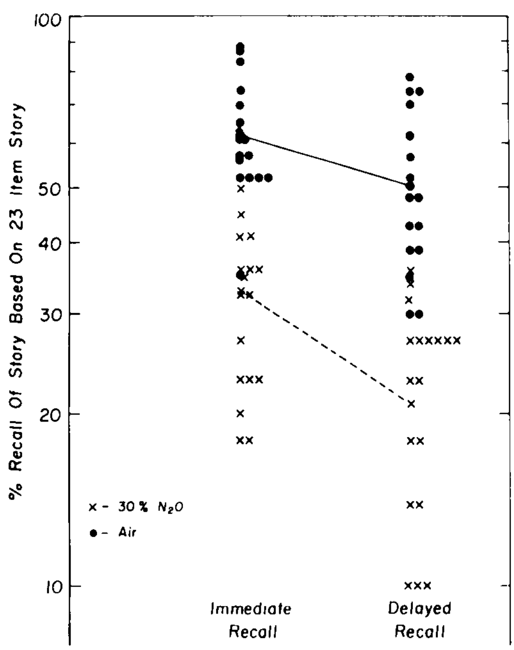

Fig. 3. Comparison of immediate and delayed recall of story with breathing of air and of 30 per cent nitrous oxide.

A tabulation was made of the data from all tests involving the meaningful stories. A mean of 14.2 among 23 items were recalled on immediate testing with air, but only 7.7 among 22 on testing with gas. Forty-five minutes after the story was heard (30 minutes after the administration of gas was discontinued), recall of items in the story was evaluated again and recognition was tested. The means for delayed recall were 11.5 items with air and 4.9 with gas.

On the recognition tests given 30 minutes after the administration of gas was discontinued, the subjects identified 17.0 of 23 items after breathing air, and 9.7 of 22 items after breathing nitrous oxide.

Introspective Reports. The 18 subjects wrote their introspective reports in response to the general headings on the paper provided immediately after the administration of gas or compressed air was discontinued. Their motivation for reporting and their capacity for introspective analysis were important variables. Since the introspective report was written near the end of the testing session, the length of the experiment tended to reduce the motivation needed for producing these data.

Four subjects, after receiving compressed air, recorded mental or physical effects that they attributed to what they had breathed. Of this symptomatic group, three described mild lightheadedness, two were euphoric, one complained of pressure from the mask, and one described a vibrating or throbbing feeling and erotic sensations.

Response to Nitrous Oxide: All of the subjects recorded physical and mental changes that occurred while they were breathing 30 per cent nitrous oxide, but the reported effects were diverse. More than half of the subjects reported mild to severe paresthesias, usually describing them as numbness or tingling in their arms and legs and occasionally around their lips. Other symptoms noted by more than 50 per cent of the group included: (1) euphoria, (2) sleepiness, (3) lightheadedness, (4) impairment of concentration, and (5) impairment of memory. Twenty-eight per cent reported auditory effects, usually as an accentuation of low tones and a sense of being cut off from the environment. Twenty-two per cent complained of nausea, and one subject vomited.

A tendency to perseverate, déjà vu phenomena, distorted perception of time, motor inco-ordination, and blurring of vision were described also by 17 to 22 per cent of the subjects; but the symptoms were of varied intensity. Compulsive laughter was observed in two subjects. One subject had a marked anxiety reaction, as did another person not included among the 18 because his profuse perspiration resulted in serious artefacts throughout the EEG record.

INFLUENCE OF PREVIOUS EXPERIENCE: It must be stated at this point that all but two of the 18 subjects participated in an analgesic study [14] (table 2) as well as in the project here reported, and nearly all of the testing in the analgesic study was completed first. Although the order of testing produced no significant differences in the results on the mental tests, differences were evident in the introspective data.

The most striking difference between the introspective reports from the analgesic study and those obtained during this experiment was that generally the subjects recorded fewer subjective effects when they received the same concentration of gas the second time. Reports of the first experience contained 1½ to 3 times as many subjective changes as the same subjects' reports of the second. It should be emphasized that the subjects did not know the concentrations of gases utilized.

EEG Data. VISUAL ANALYSIS: The two electroencephalograms from each subject—one showing the response to gas and the other to air—were read by an electroencephalographer who did not know which was the nitrous-oxide record in each pair. In six of the 18 pairs he could see no significant change; he distinguished correctly in nine pairs and erroneously in the remaining three. He found no consistent nitrous-oxide effect, but noted as prominent features the increase of theta (4 to 7 cps) activity in the motor area, paroxysmal theta activity after the administration of gas was discontinued, and minimal slowing.

STATISTICAL ANALYSIS: In the quantitative analysis of 7 to 10 minutes of the continuous record, the integrated voltage for each frequency was measured and the average of activity per minute for each band was calculated.

A summary was made of statistically significant differences between each subject's average of total activity in the 7 to 10 minutes of each selected frequency band recorded with air and his average in the corresponding band recorded with nitrous oxide (table 3). The t test was applied to determine the significance of the difference between the means. Values for p were $> .02$ to .025, and were considered significant.

CHANGES NOTED: Each subject's EEG differences were matched with the impairment of his immediate recall of the meaningful story on the test with gas (table 3). (The attempt to correlate performance data with

TABLE 3

COMPARISON OF NITROUS-OXIDE IMPAIRMENT OF STORY RECALL WITH NITROUS-OXIDE CHANGE OF ACTIVITY IN EEG FREQUENCY BANDS

Impairment of Story Recall,* Per Cent	Change of Activity in EEG Frequency Bands (cps)†‡			
	4–7	8–13	14–18	20–30
56	+	+	+	+
13	+	+	+	+
68	+	+	0	+
74	0	+	0	+
51	0	+	0	+
4	+	0	+	+
57	0	0	+	+
39	0	0	0	0
65	0	0	0	0
21	0	0	0	–
33	0	0	–	–
41	+	0	–	–
66	+	–	0	0
65	0	–	0	0
28	–	–	0	0
100	0	–	–	–
37	–	–	–	–
73	–	–	–	–

* Minus difference from score on test with air to score on test with 30 per cent nitrous oxide.

† Change from activity levels established with air to levels recorded with 30 per cent nitrous oxide: + indicates significant increase; –, significant decrease; 0, no significant change.

‡ Data for delta frequencies (1.5–3.5 cps) were excluded because eye-roll artefacts made them unreliable.

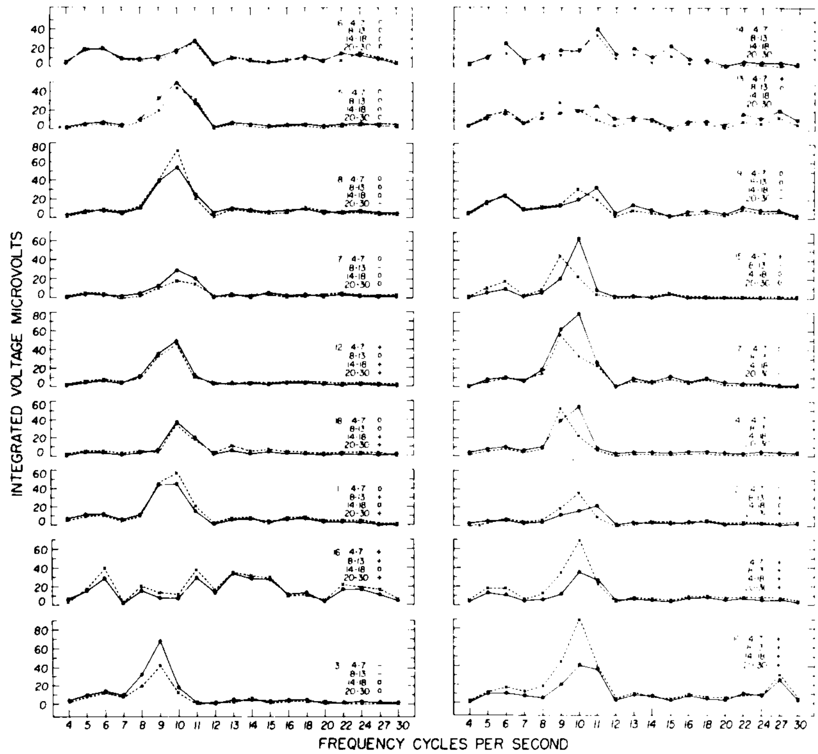

FIG. 4. Comparison of EEG profiles from period with air (• •) and period with 30 per cent nitrous oxide (x - - - x).

the EEG will be discussed later.) Inspection reveals a range from significant increase in activity in each band of frequencies to no significant change, to significant reduction in every band. The records from five subjects showed an increase in alpha activity, and an increase in beta activity was associated in all of these. Records from six showed a decrease in alpha activity, and in none of these did activity increase in faster frequencies. Indeed, this subgroup manifested a tendency toward over-all reduction in electrical activity as recorded from the cortex.

At best this method of analysis reflects shifts in total activity between the frequency bands described. Figure 4 compares 18 sets of EEG profiles, each set consisting of a profile from the EEG recorded during breathing of nitrous oxide and another from the same subject in the control situation.

Frequency shifts were evaluated by comparing the activity of the subject's peak frequencies under the two conditions. The peak frequency was defined as the frequency having the maximal integrated voltage over the 7 to 10-minute period analyzed. The graphic analysis revealed that approximately one third of the 18 pairs of profiles exhibited a shift from their peak voltage frequency with air to a peak frequency about one cycle per second slower with gas—that is, the peak frequency shifted from 10 to 9 cps or from 11 to 10.

OVERSWING: Probably one of the most striking changes seen in the records of subjects receiving 30 per cent nitrous oxide was an overswing phenomenon that occurred immediately after the removal of the mask (fig. 5). The overswing consisted of paroxysmal bursts of high-voltage theta (4 to 7 cps) activity occurring diffusely throughout the recording. It cannot be attributed entirely to drowsiness, since subjects demonstrated it whose alpha (8 to 13 cps) activity was maximal just prior to removal of the mask. The subject whose tracing is pictured in figure 5 stated that he felt "nearly normal, but somewhat distant; as though in a cloud" at the time his mask was removed and the tracing was recorded.

This paroxysmal theta activity did not occur in all subjects, and in some the theta discharge following removal of the mask was only minimally increased. Unfortunately it was a chance observation, and recordings from one third of the subjects were not continued after their masks were removed. The paroxysmal discharges of theta were never observed to occur in subjects who had received compressed air when EEG recording was continued after removal of their masks. The cause of this change is speculative. The diffuse paroxysmal nature of the theta discharges suggests a temporary change or imbalance in the thalamic-cortical regulatory system when the administration of nitrous oxide is terminated suddenly.

Variability and Correlation with other Records: The marked variability possible in electroencephalograms of normal subjects receiving nitrous oxide is further demonstrated in figure 6. Two samples of actual EEG tracings made during breathing of air and of gas are pictured. In the upper tracing no change between them could be found. Despite the absence of EEG changes, however, the subject's introspective report of her condition during the test with 30 per cent nitrous oxide was as follows:

> Legs and arms, tongue, lips, throat very numb–legs and arms felt very heavy and co-ordination (in handling test cards) was very much impaired. Vision was moderately blurred–had difficult time focusing eyes. My memory was impaired quite a lot and it took much effort to concentrate. When I was lying down, every once in a while I'd get a streak when I wanted to laugh, but I tried not to. Felt relaxed and oblivious to surroundings.

This subject's immediate recall of the story was impaired 65 per cent as compared to her recall on compressed air.

The lower tracing illustrates changes in the EEG produced in certain subjects by breathing of 30 per cent nitrous oxide. This tracing demonstrates the increase of theta (4 to 7 cps) activity, particularly in the motor area, and the shift in peak frequency from 10 to 9 cps.

As implied by the introspective and retention data reported just above from the subject with no EEG change produced by nitrous

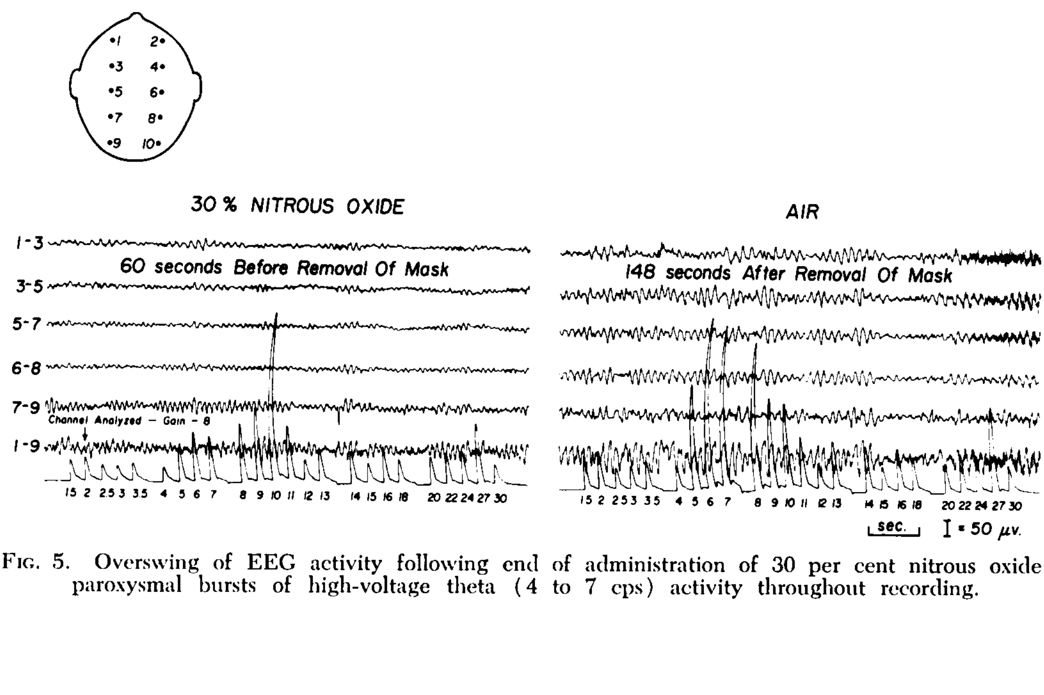

Fig. 5. Overswing of EEG activity following end of administration of 30 per cent nitrous oxide: paroxysmal bursts of high-voltage theta (4 to 7 cps) activity throughout recording.

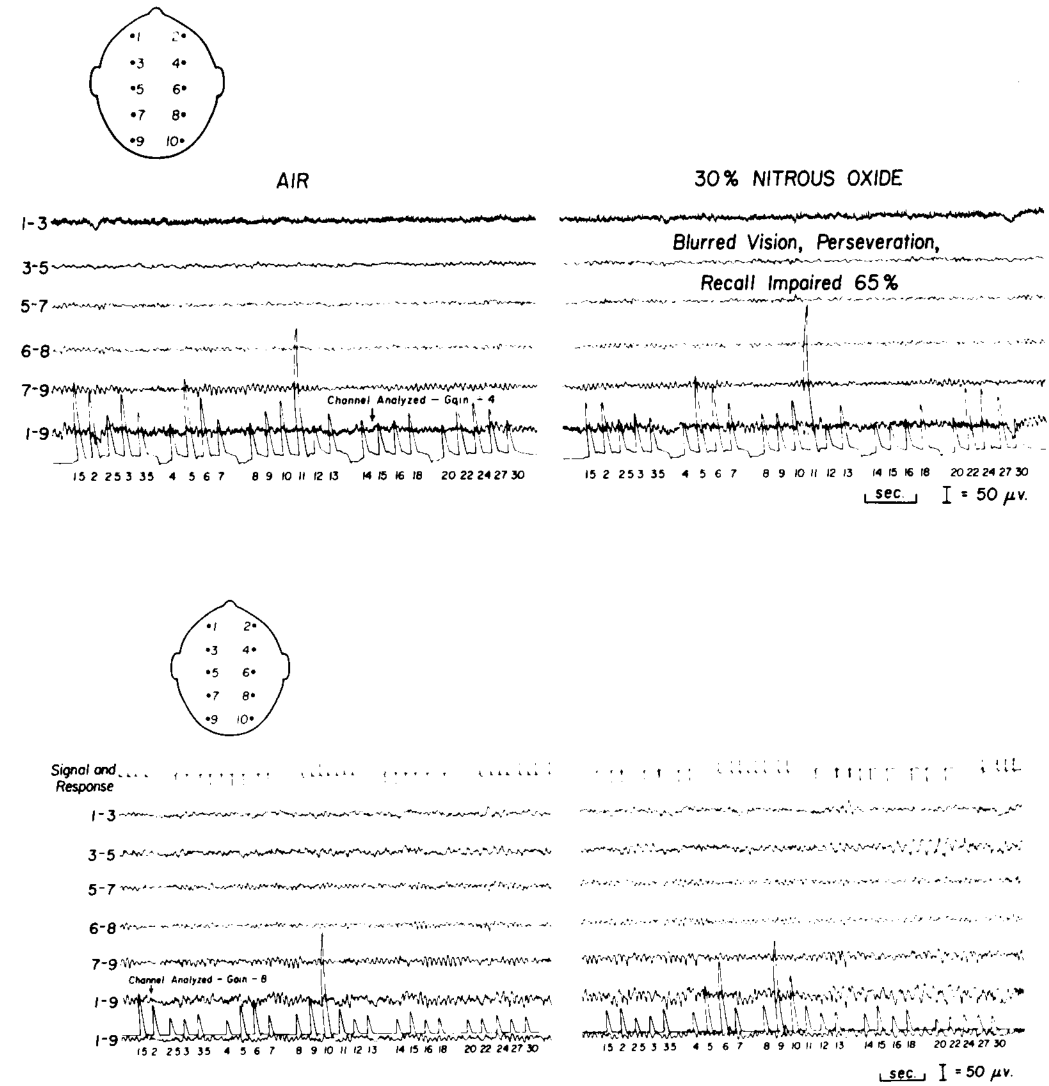

FIG. 6. Contrasting EEG responses to breathing of 30 per cent nitrous oxide. *Upper tracing:* no change from pattern established while breathing air. *Lower tracing:* increase of theta (4 to 7 cps) activity and shift of peak frequency from 10 to 9 cps; also, record of telegraph-key signal and response utilized in arousal system, which was employed constantly during control and gas recordings.

oxide, the attempt to correlate subjective changes and impairment of performance with the EEG data were not successful. Inspection of table 3 again demonstrates the lack of correlation between EEG effects of nitrous oxide and impairment of rention. The absence of any consistent EEG changes with breathing of 30 per cent nitrous oxide limited the possible value of attempts to correlate other data with the EEG. However, neither shift of frequency, diminution of alpha activity, nor increase or decrease in total recorded activity showed a significant correlation with any of the retention tests or introspective reports of the subject's degree of impairment.

COMMENT

Perhaps one of the most striking observations during the EEG recordings was the effect of drowsiness on the EEG in comparison to relative lack of effect of 30 per cent nitrous oxide. If a subject became drowsy during the recording, immediately alpha activity was partially supressed. While breathing nitrous oxide, however, the EEG effects were minimal even though many subjects demonstrated marked decrease in their ability to receive and recall the stimuli tested.

The EEG has been recommended as a sensitive index of impaired consciousness, but often the meaning of consciousness and the parameters by which it is assessed are defined vaguely by those who utilize the EEG for this purpose. In the classic papers presented in the Laurentian symposium,[16, 17] the EEG changes are correlated with the "waking state," arousal responses, and sleep. If consciousness is equated with ability to be aroused, it is made virtually an all-or-none-phenomenon. Few workers regard it thus. More probably the study of consciousness entails the challenge of assessing levels of awareness in the waking state. In sleep, a natural alteration of consciousness, the alteration may be reflected in impairment of the awareness and retention of stimuli, as earlier studies have suggested. And this change may be associated also with the classic EEG changes apparent with varying depths of sleep.

However, there are numerous exceptions to the studies that have demonstrated a correlation in disorders of consciousness and EEG changes. Gastaut[16] thought "that the state of psychic activity and that of the EEG are independent of each other, but that they both depend upon a third factor: their subcortical control. This is why they generally develop in the same direction but at times they may show marked discrepancies."

The lack of demonstrable effect of 30 per cent nitrous oxide on the electroencephalograms of some of the subjects was an unexpected finding. Recent investigations on the site of action of anesthetic agents may partially clarify the relative insensitivity of the EEG to rather moderate concentrations of nitrous oxide. The EEG records made through the skull are thought to express the activity of cortical neurones rather than that of afferent axons. Adrian[17] noted that in barbiturate anesthesia surface records from the sensory area of the cat's brain may show complete lack of correspondence with records of the afferent discharges which reach it. The Arduinis[18] confirmed the results of earlier investigators in showing the great susceptibility of the reticular formation of the brain stem to anesthetic and depressant drugs. They postulated that the complexity of internal organization of a part of the brain and in particular the intricacy of its synaptic interconnections are primary factors in determining its differential sensitivity to drugs and metabolic changes. The minimal EEG changes observed with nitrous oxide in this study suggest that other areas may be more sensitive to light concentrations of the gas than are the cortical neurones.

Along with the results from this experiment presented in table 2 are data from comparable mental tests given in an earlier analgesic study[15] using nitrous oxide. The similarity of results obtained in these two rather different experiments suggests that the degree of impairment evident in both series of cases is related to the breathing of the gas rather than to variables in the test materials or procedures.

Since 70 per cent oxygen was used with the nitrous oxide, the question arises whether any of the observed EEG changes were due to the high concentration of oxygen. Gibbs and associates[19] studied the effects of high concentrations of oxygen on the EEG. They had to use rabbits rather than men because the high oxygen pressure necessary to produce marked changes in the cortical spectra was difficult to maintain and control properly for an animal so large as man. They reported that little change occurred until an oxygen pressure of approximately 35 pounds per square inch was reached. At this point they noted a sudden shift toward the fast side of the spectrum with an apparent increase in total energy. However, Engel and coworkers[20] reported that inhaling 100 per cent oxygen results in a slight but significant shift toward faster rhythms in the cortical frequency spectra. In the present study, data on rich concentrations of oxygen are not sufficient to determine whether the increase in faster frequencies observed in some of the subjects was due to the high concentration of oxygen. In two subjects evaluated repeatedly in the preliminary trials, no increase in fast activity was seen with pure oxygen.

A nonrebreathing mask was used to guard against accumulation of carbon dioxide, and the subjects were watched closely to prevent hyperventilation. All subjects ate within one or two hours before the EEG study, so the possibility that the EEG was altered by deficiency of blood sugar seemed minimal.

Clearly the psychologic tests gave a more consistent pattern of change with nitrous oxide than the EEG records did. Each of the three tests sensitively reflected the marked deterioration in performance of the group with breathing of gas. (As anticipated, the recognition appeared to indicate greater retention than did recall, since the memory cues in the recall method of assessing retention are minimal compared to those in the methods used for testing recognition.) However, the marked variation in the sensitivity of different subjects to nitrous oxide was impressive.

According to Luh's[13] classic monograph on retention, the time interval (45 minutes) between immediate and delayed testing on the story would fall in the steepest part of the curve on "forgetting." Obviously the interval in which the degree of forgetting changes rapidly is an undesirable choice for investigations of this kind, for the rapidity of general change magnifies individual variability. However, essential practical considerations made a longer interval impossible in this experiment. It might be informative to study the amnesic effects of nitrous oxide with a longer interval after administration of nitrous oxide and to assess the retention of affect-laden as well as more neutral stimuli. In preliminary trials using 50 and 60 per cent concentrations of the gas, meaningful stimuli were retained with surprising detail by certain subjects. This problem, however, awaits future investigation; for our present data on the effects of higher concentrations of the gas are inadequate.

Also, the degrees of euphoria, distractibility, dissociation, and in some subjects pervasive suspiciousness were important variables that made the performance while breathing gas not predictable from the control score. Frequently the subjects whose performance was most impaired revealed also the most marked behavioral effects of the gas. Certainly physiologic effects of gas—and particularly the alteration in an individual's perception of himself and his environment that is associated with the gas, as well as personality differences—are interwoven factors in producing the psychic manifestations seen with nitrous oxide.

Summary

The impairment of consciousness produced by breathing of 30 per cent nitrous oxide was evaluated in 18 normal subjects on the basis of (1) retention tests, (2) introspective reports, and (3) the EEG.

The verbal and visual retention tests revealed marked impairment between performances of the group when breathing air and when breathing gas. Variations in the responses to nitrous oxide were marked.

Although each test revealed significant changes under nitrous oxide, the correlation between tests was low. This finding points to an important limitation in use of retention tests to evaluate alteration of consciousness.

The introspective physic effects of nitrous oxide seemed to reflect the subjects' impaired perception of their environment as well as temperamental instabilities.

Amnesic effects apparently were due to defect in registration of the stimulus. Delayed recall (45 minutes after learning under gas) was minimally impaired.

EEG tracings recorded from each subject in the experiments with gas and in control procedures with air and analyzed visually and automatically revealed no consistent EEG difference due to nitrous oxide. Neither changes in alpha activity nor frequency shifts could be correlated with the impairment recorded on the mental tests.

Several subjects' paroxysmal bursts of diffuse theta activity immediately following change from gas to air may have reflected disturbance of an adjustment that had been established in the thalamic-cortical control system.

The physcologic tests provided a more uniform measure of gaseous effects than did the EEG.

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